PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

VAXNEUVANCE®

(Pneumococcal 15-valent Conjugate Vaccine [CRM_{197} Protein], adsorbed)

Suspension for injection

Active immunizing agent

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RECENT MAJOR LABEL CHANGES
Not applicable

TABLE OF CONTENTS

Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

VAXNEUVANCE® (Pneumococcal 15-valent Conjugate Vaccine [CRM_{197} Protein], adsorbed) is indicated for the active immunization of adults 18 years of age and older for the prevention of invasive disease (including sepsis, meningitis, bacteremic pneumonia, pleural empyema and bacteremia) caused by *Streptococcus pneumoniae* serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F).

VAXNEUVANCE® may not prevent disease caused by *S. pneumoniae* serotypes that are not contained in the vaccine.

1.1 Pediatrics (< 18 years of age)

The safety and effectiveness of VAXNEUVANCE® in individuals younger than 18 years of age have not yet been established.

1.2 Geriatrics (≥ 65 years of age)

VAXNEUVANCE® has been studied in the geriatric population (see 7.1 Special Populations, 14 Clinical Trials).

2 CONTRAINDICATIONS

VAXNEUVANCE® is contraindicated in individuals with a history of a severe allergic reaction (e.g., anaphylaxis) to any component of the vaccine or any diphtheria toxoid-containing vaccine. (see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING).

4 DOSAGE AND ADMINISTRATION

4.2 Recommended Dose and Dosage Adjustment

Administer a 0.5 mL dose of VAXNEUVANCE® intramuscularly.

Adults

One single dose (0.5 mL).

Pediatrics

Health Canada has not authorized an indication for pediatric use.

4.4 Administration

For intramuscular use only. Do not inject intravascularly.

The preferred site for injection is the deltoid muscle of the upper arm in adults. The vaccine should not be injected in the gluteal area or areas where there may be a major nerve trunk and/or blood vessel.

Instructions for use:

VAXNEUVANCE® should not be diluted or mixed with other vaccines. The full recommended dose of the vaccine should be used.

When VAXNEUVANCE® is administered at the same time as another injectable vaccine(s), the vaccines should always be given at different injection sites (see 9.4 Drug-Drug Interactions, Use with Other Vaccines)**.**

Because this product is a suspension containing an adjuvant, hold horizontally and shake vigorously immediately prior to use to obtain an opalescent suspension in the vaccine container. Do not use the vaccine if it cannot be resuspended. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. This product should not be used if particulate matter or discoloration is found.

The prefilled syringe is for single use only and should not be used for more than one individual. Attach a needle by twisting in a clockwise direction until the needle fits securely on the syringe. Inject the entire contents of the syringe. Exercise caution to avoid harm from an accidental needle stick.

4.5 Missed Dose

Not Applicable. This vaccine is administered as a single dose.

5 OVERDOSAGE

There are no data with regard to overdose.

For management of a suspected vaccine overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

To help ensure the traceability of vaccines for patient immunization record-keeping as well as safety monitoring, health professionals should record the time and date of administration, quantity of administered dose (if applicable), anatomical site and route of administration, brand name and generic name of the vaccine, the product lot number and expiry date.

VAXNEUVANCE® is a suspension for injection available in 0.5 mL single-dose prefilled syringes.

The vaccine is an opalescent suspension.

Available in pack sizes of 1 or 10 prefilled syringes with or without needles.

The tip cap and plunger stopper of the prefilled syringe are latex free.

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intramuscular injection	Suspension for injection Each 0.5 mL dose contains 32 mcg of total pneumococcal polysaccharide (2.0 mcg each of polysaccharide serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, and 33F, and 4.0 mcg of polysaccharide serotype 6B) conjugated to 30 mcg of CRM_{197} carrier protein.	Each 0.5 mL dose contains 125 mcg of aluminum (as aluminum phosphate adjuvant), 20 mM L-histidine, 1 mg of polysorbate 20, 150 mM sodium chloride and water for injection. VAXNEUVANCE® does not contain any preservatives.

7 WARNINGS AND PRECAUTIONS

General

As with any vaccine, VAXNEUVANCE® may not protect all vaccine recipients.

Minor illnesses, such as mild respiratory infection, with or without low-grade fever, are not generally contraindications to vaccination. The decision to administer or delay vaccination because of a current or recent febrile illness depends largely on the severity of the symptoms and their etiology. The administration of VAXNEUVANCE® should be postponed in subjects suffering from acute severe febrile illness.

Immune

Individuals with altered immunocompetence, including those receiving immunosuppressive therapy, may have a reduced immune response to VAXNEUVANCE® (see 9.4 Drug-Drug Interactions, Use with Immunosuppressive Therapies).

7.1 Special Populations

7.1.1 Pregnant Women

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/foetal development, parturition or post-natal development (see 16 Non-Clinical Toxicology).

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. There are no adequate and well-controlled studies of VAXNEUVANCE® in pregnant women. Available data on VAXNEUVANCE® administered to pregnant women are insufficient to inform vaccine-associated risks in pregnancy. The decision to vaccinate a woman who is pregnant should consider the woman's risk of exposure to *S. pneumoniae*; VAXNEUVANCE® should be administered only if clearly needed.

7.1.2 Breast-feeding
It is not known whether this vaccine is excreted in human milk.

7.1.3 Pediatrics (< 18 years of age)
The safety and effectiveness of VAXNEUVANCE® in individuals younger than 18 years of age have not yet been established.

7.1.4 Geriatrics (≥ 65 years of age)
Of the 4,344 individuals aged 50 years and older who received VAXNEUVANCE®, 2,470 (56.9%) were 65 years and older, and 479 (11.0%) were 75 years and older (see 8.2 Clinical Trial Adverse Reactions and 14 Clinical Trials).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview
The safety of VAXNEUVANCE® in healthy and immunocompetent adults was assessed in 6 clinical studies in 7,136 adults ≥ 18 years of age. VAXNEUVANCE® was administered to 5,478 adults including those previously vaccinated with PPV23. The most frequently (≥5%) reported adverse reactions following vaccination with VAXNEUVANCE® were solicited and included pain, erythema, and swelling at the injection site, fatigue, headache, arthralgia, and myalgia. Older adults reported fewer solicited adverse reactions than younger adults. The majority of solicited adverse reactions were mild (based on intensity or size) and of short duration (≤ 3 days); severe reactions (defined as an event that prevents normal daily activity or size > 10 cm) occurred in ≤ 1.5% of adults.

8.2 Clinical Trial Adverse Reactions
Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

The safety of VAXNEUVANCE® in healthy and immunocompetent adults was assessed in 6 randomized, double-blind clinical studies (Protocol 007, Protocol 016, Protocol 017, Protocol 019, Protocol 020 and Protocol 021) conducted across the Americas, Europe and Asia Pacific, which included 7,136 adults ranging in age from 18 to 98 years. Each study enrolled adults with stable underlying medical conditions (e.g., diabetes mellitus, renal disorders, chronic heart disease, chronic liver disease, chronic lung disease including asthma) and/or risk factors (e.g., smoking, increased alcohol use) that are known to increase the risk of pneumococcal disease. The mean age of the participants was 59 years and 56.0% were female. The racial distribution was as follows: 74.1% were White, 9.6% were Asian, 8.5% were American Indian or Alaska Native, 6.4% were Black or African American, and 17.6% were of Hispanic or Latino ethnicity.

VAXNEUVANCE® was administered to 5,478 adults; 1,134 were 18 to 49 years of age, 1,874 were 50 to 64 years of age, and 2,470 were 65 years of age and older. Of those who received VAXNEUVANCE®, 5,101 adults were pneumococcal vaccine-naïve and 377 adults were previously vaccinated with PNEUMOVAX®23 at least 1 year prior to enrollment.

The safety of VAXNEUVANCE® in pneumococcal vaccine-naïve adults 50 years of age and older was evaluated in 3 active comparator-controlled clinical studies (Protocol 016, Protocol 019 and

Protocol 020) in which 3,032 participants received VAXNEUVANCE® and 1,154 participants received Prevnar*13. A descriptive study (Protocol 017 evaluated the safety of VAXNEUVANCE® in pneumococcal vaccine-naïve adults 18 to 49 years of age.

The safety of VAXNEUVANCE® in adults 65 years of age and older who were previously vaccinated with PNEUMOVAX®23 (at least 1 year prior to study entry) was evaluated in an additional descriptive study (Protocol 007).

The safety of concomitant administration of VAXNEUVANCE® with seasonal inactivated influenza vaccine was evaluated in 1,196 adults 50 years of age and older, including those with or without a history of prior vaccination with PNEUMOVAX®23 (Protocol 021).

Safety was evaluated using a Vaccination Report Card for up to 14 days postvaccination. Oral body temperature and injection-site adverse events were solicited on Day 1 through Day 5 postvaccination. Systemic adverse events were solicited on Day 1 through Day 14 postvaccination. Unsolicited adverse events were reported on Day 1 through Day 14 postvaccination. The duration of the safety follow-up period postvaccination with VAXNEUVANCE® was 1 month in Protocol 007, 6 months in Protocol 019, Protocol 020, Protocol 017 and Protocol 021 and 12 months in Protocol 016.

Solicited Adverse Reactions

The percentage of participants with solicited adverse reactions that occurred within 5 or 14 days following administration of VAXNEUVANCE® or Prevnar*13 in 4 studies are shown in Table 2.

Table 2 – Percentage of Participants with Solicited Local and Systemic Adverse Reactions Within 5 or 14 Days Postvaccination in Pneumococcal Vaccine-Naïve Adults

	Protocol 019		Protocol 020		Protocol 016		Protocol 017	
Age in Years	≥50						18-49	
	VAXNEUVANCE® (%) N=602	**PCV13 (%) N=600**	**VAXNEUVANCE® (%) N=2103**	**PCV13 (%) N=230**	**VAXNEUVANCE® (%) N=327**	**PCV13 (%) N=324**	**VAXNEUVANCE® (%) N=1134**	**PCV13 (%) N=378**
Local Reactions[a]								
Pain	54.0	42.3	66.8	52.2	55.0	41.4	75.8	68.8
Erythema	9.0	11.3	10.9	9.6	9.8	5.6	15.1	14.0
Swelling	12.5	11.2	15.4	14.3	16.2	11.4	21.7	22.2
Systemic Reactions[†]								
Fatigue	17.4	17.3	21.5	22.2	23.5	13.9	34.3	36.8
Headache	11.6	13.0	18.9	18.7	14.1	12.7	26.5	24.9
Myalgia	15.4	12.0	26.9	21.7	17.7	11.1	28.8	26.5
Arthralgia	5.3	5.5	7.7	5.7	6.4	5.2	12.7	11.6
Elevated Body Temperature*[‡]								
≥38.0°C and <39.0°C	0.3	1.3	0.7	0.4	0.6	0.6	1.3	0.3
≥39.0°C	0.2	0.0	0.0	0.0	0.6	0.6	0.2	0.0

[a] Solicited on Day 1 through Day 5 postvaccination
[†] Solicited on Day 1 through Day 14 postvaccination
[‡] Percentages are based on the number of participants with temperature data
N=Number of participants vaccinated

The safety profile of VAXNEUVANCE® in adults previously vaccinated with PPV23 (Protocol 007) was generally consistent with its safety profile in pneumococcal vaccine-naïve adults.

Additional information in special populations

Populations at increased risk for pneumococcal disease

Adults living with HIV

In adults living with HIV (Protocol 018), the safety profile of VAXNEUVANCE® was consistent with the safety profile in immunocompetent pneumococcal vaccine-naïve adults.

Adults with chronic conditions and other risk factors

In adults 18 to 49 years of age with 1 risk factor or 2 or more risk factors for pneumococcal disease (Protocol 017), the safety profile of VAXNEUVANCE® was generally consistent with its safety profile in the overall study population.

Safety with Concomitant Influenza Vaccine Administration

The safety profile of VAXNEUVANCE® when administered concomitantly with inactivated influenza vaccine was generally consistent with the safety profile of VAXNEUVANCE®.

8.3 Less Common Clinical Trial Adverse Reactions
Less frequently reported (<5%) adverse reactions were unsolicited and included injection-site pruritis which occurred in 1.0% to 2.8% of pneumococcal vaccine-naïve adults vaccinated with VAXNEUVANCE®.

8.5 Post-Market Adverse Reactions
There are no post-marketing data available for VAXNEUVANCE®.

9 DRUG INTERACTIONS

9.4 Drug-Drug Interactions
Use with Other Vaccines
VAXNEUVANCE® can be administered concomitantly with inactivated influenza vaccine (see 8.2 Clinical Trial Adverse Reactions and 14 Clinical Trials). There are no data on the concomitant administration of VAXNEUVANCE® with other vaccines.

Use with Immunosuppressive Therapies
Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs, corticosteroids, therapeutic proteins and targeted immunomodulators may reduce the immune responses to vaccines (see 7 Warnings and Precautions).

9.5 Drug-Food Interactions
Not Applicable.

9.6 Drug-Herb Interactions
Not Applicable.

9.7 Drug-Laboratory Test Interactions
Not Applicable.

10 CLINICAL PHARMACOLOGY

Therapeutic Class
VAXNEUVANCE® is a conjugated polysaccharide vaccine that protects against invasive disease and pneumonia caused by *Streptococcus pneumoniae*.

10.1 Mechanism of Action
VAXNEUVANCE® contains serotype-specific pneumococcal capsular polysaccharides each of which is conjugated to a carrier protein (CRM_{197}), and elicits antibodies that enhance opsonization, phagocytosis, and killing of pneumococci to protect against pneumococcal disease. VAXNEUVANCE® elicits a T-cell dependent immune response. Carrier protein-specific helper T-cells support specificity, functionality and maturation of serotype-specific B cells.

Immune responses following natural exposure to *S. pneumoniae* or following pneumococcal vaccination can be determined through the measurements of OPA and IgG responses. OPA represents functional antibodies capable of opsonizing pneumococcal capsular polysaccharides for presentation to phagocytic cells for engulfment and subsequent killing and are considered an important immunologic

surrogate measure of protection against pneumococcal disease in adults. OPA titers are expressed as the reciprocal of the highest serum dilution that reduces survival of the pneumococci by at least 50%. A validated multiplexed opsonophagocytic assay (MOPA) was used to measure serotype-specific OPA titers for each of the 15 serotypes contained in VAXNEUVANCE®.

10.3 Pharmacokinetics

Duration of Effect

Duration of effect was evaluated up to 12 months postvaccination with VAXNEUVANCE®. Immune responses elicited by VAXNEUVANCE® persisted up to 12 months postvaccination as assessed by OPA GMTs and IgG GMCs. Immune responses at 12 months postvaccination were comparable between VAXNEUVANCE® and Prevnar*13 for the 13 shared serotypes and higher in VAXNEUVANCE® for the 2 unique serotypes.

10.4 Burden of Disease

Adults

Pneumococcal disease is associated with significant morbidity and mortality in both children and adults worldwide. Although all age groups may be affected by pneumococcal disease, the highest rates of disease occur in young children <5 years of age and adults ≥65 years of age. In addition, mortality rates are elevated in older adults, adults with comorbid conditions (e.g., diabetes mellitus, chronic lung disease, chronic liver disease), and especially immunocompromised individuals (e.g., HIV infection, cancer, transplant, immunosuppressive therapies). Adults with 2 or more comorbid conditions may have a risk of pneumococcal disease that is comparable to immunocompromised individuals.

Clinical syndromes include both invasive pneumococcal disease (IPD) (i.e. sepsis, meningitis, and bacteremic pneumonia) and noninvasive disease (e.g., non-bacteremic pneumonia). Pneumococcal pneumonia is the most frequent presentation of IPD in adults, with bacteremic pneumonia accounting for the majority of IPD cases. Community acquired pneumonia (CAP) remains one of the most important causes of death from infection in many countries, with S. pneumoniae being one of the most commonly identified bacterial pathogens.

Following childhood immunization programs using Prevnar*7, (PCV7, 7-valent conjugate vaccine) and subsequently replaced by Prevnar*13 (PCV13, 13-valent conjugate vaccine), the incidence of pneumococcal disease due to serotypes included in current vaccines, excluding serotype 3, had decreased through direct protection in children and indirect protection in adults. Despite the significant public health impact of currently available pneumococcal vaccines, pneumococcal disease remains a significant unmet medical need.

11 STORAGE, STABILITY AND DISPOSAL

Store refrigerated at 2°C to 8°C.
Do not freeze. Protect from light.

VAXNEUVANCE® should be administered as soon as possible after being removed from the refrigerator.

12 SPECIAL HANDLING INSTRUCTIONS

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance
VAXNEUVANCE®: (Pneumococcal 15-valent Conjugate Vaccine [CRM_{197} Protein], adsorbed)

Physicochemical properties: The vaccine is an opalescent suspension.

Product Characteristics:
VAXNEUVANCE® (Pneumococcal 15-valent Conjugate Vaccine [CRM_{197} Protein], adsorbed) is a sterile suspension of purified capsular polysaccharides from *S. pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, and 33F individually conjugated to CRM_{197}. Each pneumococcal polysaccharide is activated via sodium metaperiodate oxidation and then individually conjugated to CRM_{197} carrier protein via reductive amination. CRM_{197} is a nontoxic mutant of diphtheria toxin (originating from *Corynebacterium diphtheriae* C7) expressed recombinantly in *Pseudomonas fluorescens*.

Each of the fifteen serotypes is manufactured independently using a common manufacturing platform with slight variations to accommodate for differences in strains, polysaccharides and process stream properties. The process consists of the fermentation steps to produce the inactivated pneumococcal bacteria and the purification process which consists of clarification, ultrafiltration, polishing and recovery to produce purified polysaccharides. Each activated polysaccharide is conjugated to lysine groups on the CRM_{197} carrier protein using reductive amination. The pneumococcal polysaccharide powder is dissolved, size reduced to a target molecular mass, chemically activated, and buffer-exchanged by ultrafiltration. The CRM_{197} protein carrier is then conjugated to the activated pneumococcal polysaccharide. The final vaccine is prepared by blending the fifteen conjugates with aluminum phosphate adjuvant in a final buffer containing histidine, polysorbate 20 and sodium chloride.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Table 3 - Summary of patient demographics for clinical trials for Pneumococcal Disease Immunogenicity and Safety

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
P007	Randomized, double-blind, active comparator-controlled, multicenter study to evaluate the safety, tolerability, and immunogenicity of VAXNEUVANCE®	1 dose of 0.5 mL VAXNEUVANCE® or Prevnar*13 Intramuscular injection	253	72,7 years (65 to 96 years)	Females: 151 Males: 102
P016	Randomized, double-blind, active comparator-controlled, multicenter study to evaluate the sequential administration of VAXNEUVANCE® followed by PPV23 one year later	1 dose of 0.5 mL VAXNEUVANCE® or Prevnar*13 and PNEUMOVAX®23	651	64,1 years (50 to 90 years)	Females: 370 Males: 281
P017	Randomized, double-blind, active comparator-controlled, multicenter study to evaluate the safety, tolerability, and immunogenicity of VAXNEUVANCE® followed by PPV23 six months later	1 dose of 0.5 mL VAXNEUVANCE® or Prevnar*13 followed by PNEUMOVAX®23 six months later	1512	35,8 years (18 to 49 years)	Females: 781 Males: 731
P018	Randomized, double-blind, active comparator-controlled, multicenter study to evaluate the safety, tolerability, and immunogenicity of VAXNEUVANCE® followed by PPV23 eight weeks later in adults infected with HIV	1 dose of 0.5 mL VAXNEUVANCE® or Prevnar*13 followed by PNEUMOVAX®23 eight weeks later	302	41,9 years (21 to 74 years)	Females: 64 Males: 238
P019	Randomized, double-blind, active comparator-controlled, multicenter study to evaluate the safety, tolerability, and immunogenicity of VAXNEUVANCE®	1 dose of 0.5 mL VAXNEUVANCE® or Prevnar*13	1202	65,9 years (50 to 92 years)	Females: 689 Males: 513

P020	Randomized, double-blind, active comparator-controlled, multicenter, lot consistency study to evaluate the safety, tolerability, and immunogenicity of VAXNEUVANCE® across lots	1 dose of 0.5 mL VAXNEUVANCE® or Prevnar*13	2333	64,4 years (50 to 92 years)	Females: 1343 Males: 990
P021	Randomized, double-blind, placebo-controlled, multicenter study to evaluate safety, tolerability, and immunogenicity of VAXNEUVANCE® when administered concomitantly with inactivated influenza vaccine	Group 1 One dose of QIV‡ + VAXNEUVANCE® followed 1 month later by placebo Group 2 One dose of QIV‡ + placebo followed 1 month later by VAXNEUVANCE®	1197	64,2 years (50 to 98 years)	Females: 672 Males: 525
# Route of administration: Intramuscular injection in all clinical trials ‡ QIV = Quadrivalent Influenza Vaccine					

14.4 Immunogenicity

Six double-blind, clinical studies (Protocol 007, Protocol 016, Protocol 017, Protocol 019, Protocol 020 and Protocol 021) conducted across the Americas, Europe and Asia Pacific evaluated the immunogenicity of VAXNEUVANCE® in healthy and immunocompetent adults across different age groups including individuals with or without previous pneumococcal vaccination. The clinical studies included adults with stable underlying medical conditions (e.g., diabetes mellitus, renal disorders, chronic heart disease, chronic liver disease, chronic lung disease including asthma) and/or behavioral risk factors (e.g., smoking, increased alcohol use) that are known to increase the risk of pneumococcal disease. The mean age of the participants was 59 years and 56.0% were female. The racial distribution was as follows: 74.1% were White, 9.6% were Asian, 8.5% were American Indian or Alaska Native, 6.4% were Black or African American, and 17.6% were of Hispanic or Latino ethnicity.

In each study, immunogenicity was assessed by serotype-specific opsonophagocytic activity (OPA) and immunoglobulin G (IgG) responses at 30 days postvaccination. Protocol 019 was the pivotal study and endpoints included OPA geometric mean titers (GMTs) and IgG geometric mean concentrations (GMCs). For the 13 shared serotypes (in common between VAXNEUVANCE® and Prevnar*13) noninferiority was assessed based on the lower bound of the 2-sided 95% confidence interval of the OPA GMT ratio between VAXNEUVANCE® and Prevnar*13 to be greater than 0.5. For the 2 unique serotypes to VAXNEUVANCE®, 22F and 33F, and for shared serotype 3, superiority was assessed based on the between-group comparisons of OPA GMTs and proportions of participants with a ≥4-fold rise in serotype-specific OPA titers from prevaccination to 30 days postvaccination.

Clinical Trials Conducted in Pneumococcal Vaccine-Naïve Adults

In the pivotal, double-blind, active comparator-controlled study (Protocol 019), 1,205 pneumococcal vaccine-naïve adults aged 50 years or older were randomized to receive either VAXNEUVANCE® or Prevnar*13. The study demonstrated that VAXNEUVANCE® is noninferior to Prevnar*13 for the 13 shared serotypes and superior for the 2 unique serotypes and for shared serotype 3.

Table 4 summarizes the OPA GMTs at 30 days postvaccination. Serotype-specific IgG GMCs were generally consistent with the results observed for the OPA GMTs.

Table 4 - Serotype-Specific OPA GMTs in Pneumococcal Vaccine-Naïve Adults ≥50 Years of Age (Protocol 019)

Pneumococcal Serotype	VAXNEUVANCE® (N = 602)		Prevnar*13 (N = 600)		GMT Ratio[a] (VAXNEUVANCE®/Prevnar*13) (95% CI)[a]
	n	GMT[a]	n	GMT[a]	
13 Shared Serotypes[†]					
1	598	256.3	598	322.6	0.79 (0.66, 0.96)
3[‡]	598	216.2	598	135.1	1.60 (1.38, 1.85)
4	598	1125.6	598	1661.6	0.68 (0.57, 0.80)
5	598	447.3	598	563.5	0.79 (0.64, 0.98)
6A	596	5407.2	598	5424.5	1.00 (0.84, 1.19)
6B	598	4011.7	598	3258.2	1.23 (1.02, 1.48)
7F	597	4617.3	598	5880.6	0.79 (0.68, 0.90)
9V	598	1817.3	597	2232.9	0.81 (0.70, 0.94)
14	598	1999.3	598	2656.7	0.75 (0.64, 0.89)
18C	598	2757.7	598	2583.7	1.07 (0.91, 1.26)
19A	598	3194.3	598	3979.8	0.80 (0.70, 0.93)
19F	598	1695.1	598	1917.8	0.88 (0.76, 1.02)
23F	598	2045.4	598	1740.4	1.18 (0.96, 1.44)
2 Serotypes Unique to VAXNEUVANCE®[§]					
22F	594	2375.2	586	74.6	31.83 (25.35, 39.97)
33F	598	7994.7	597	1124.9	7.11 (6.07, 8.32)

[a] GMTs, GMT ratio, and 95% CI are estimated from a cLDA model

[†] A conclusion of non-inferiority for the 13 shared serotypes is based on the lower bound of the 95% CI for the estimated GMT ratio (VAXNEUVANCE®/Prevnar*13) being > 0.5.

[‡] A conclusion of superiority for serotype 3 is based on the lower bound of the 95% CI for the estimated GMT ratio (VAXNEUVANCE®/Prevnar*13) being > 1.2.

[§] A conclusion of superiority for the 2 unique serotypes is based on the lower bound of the 95% CI for the estimated GMT ratio (VAXNEUVANCE®/Prevnar*13) being > 2.0.

N=Number of participants randomized and vaccinated; n=Number of participants contributing to the analysis.

CI=confidence interval; cLDA=constrained longitudinal data analysis; GMT=geometric mean titer (1/dil); OPA=opsonophagocytic activity

In a double-blind, lot consistency study (Protocol 020), 2,340 pneumococcal vaccine-naïve adults 50 years of age and older were randomized in a 3:3:3:1 ratio to receive 1 of 3 lots of VAXNEUVANCE®

or Prevnar*13. The study demonstrated that all 3 lots are equivalent as the lower and upper limits of the 95% CI of the serotype-specific OPA GMT ratios between any 2 lots were within the equivalence margin (0.5 to 2.0) for all 15 serotypes. Immune responses following vaccination with VAXNEUVANCE® were numerically similar to Prevnar*13 for the shared serotypes.

In a double-blind, descriptive study (Protocol 017), 1,515 immunocompetent adults 18 to 49 years of age, with or without risk factors for pneumococcal disease were randomized 3:1 to receive either VAXNEUVANCE® or Prevnar*13, followed by PNEUMOVAX®23 six months later. VAXNEUVANCE® elicited immune responses to all 15 serotypes as assessed by OPA GMTs and IgG GMCs. OPA GMTs and IgG GMCs were numerically similar between the two vaccination groups for the 13 shared serotypes and higher in VAXNEUVANCE® for the 2 unique serotypes. Following vaccination with PNEUMOVAX®23, OPA GMTs and IgG GMCs were numerically similar between the two vaccination groups for all 15 serotypes in VAXNEUVANCE®.

Immune responses in adults with no risk factors (n=285; 25.2%) who received VAXNEUVANCE® were generally consistent with those observed in the overall study population.

Sequential Administration of Pneumococcal Vaccines in Adults

In a double-blind, active, comparator-controlled study (Protocol 016), 652 pneumococcal vaccine-naïve adults 50 years of age and older were randomized to receive either VAXNEUVANCE® or Prevnar*13, followed by PNEUMOVAX®23 one year later. Following vaccination with PNEUMOVAX® 23, OPA GMTs and IgG GMCs were numerically similar between the two vaccination groups for all 15 serotypes in VAXNEUVANCE®.

Immune responses elicited by VAXNEUVANCE® persisted up to 12 months postvaccination as assessed by OPA GMTs and IgG GMCs. Immune responses at 30 days and 12 months postvaccination were numerically similar between the two vaccination groups for the 13 shared serotypes and higher in VAXNEUVANCE® for the 2 unique serotypes.

The sequential administration of VAXNEUVANCE® followed by PNEUMOVAX®23 was evaluated with an interval of 2 months in immunocompromised individuals (Protocol 018) and an interval of 6 months in immunocompetent individuals with or without risk factors for pneumococcal disease (Protocol 017). (see Clinical Immunogenicity in Special Populations).

Clinical Trials Conducted in Adults with Prior Pneumococcal Vaccination

In a double-blind, descriptive study (Protocol 007), 253 adults 65 years of age and older who were previously vaccinated with PNEUMOVAX®23 at least 1 year prior to study entry were randomized to receive either VAXNEUVANCE® or Prevnar 13. IgG GMCs and OPA GMTs were numerically similar between the vaccination groups for the 13 shared serotypes and higher in VAXNEUVANCE® for the 2 unique serotypes.

Clinical immunogenicity in Special Populations

Populations at increased risk for pneumococcal disease

Adults with chronic conditions and other risk factors

In the double-blind, descriptive study (Protocol 017), the immunogenicity of VAXNEUVANCE® was evaluated in a subset of immunocompetent adults 18 to 49 years of age with one or more of the

following risk factors for pneumococcal disease: diabetes mellitus, chronic heart disease including heart failure, chronic liver disease with compensated cirrhosis, chronic lung disease including persistent asthma and chronic obstructive pulmonary disease (COPD), current tobacco use and increased alcohol consumption.

Of those who received VAXNEUVANCE®, 54.7% (n=620) had 1 risk factor and 20.1% (n=228) had 2 or more risk factors. In both of these risk factor subgroups, VAXNEUVANCE® elicited immune responses to all 15 serotypes contained in the vaccine as assessed by OPA GMTs and IgG GMCs at 30 days postvaccination, which were generally consistent with those observed in the overall study population. Sequential administration of VAXNEUVANCE® followed 6 months later by PPV23 was also immunogenic for all 15 serotypes contained in the vaccine.

Adults living with HIV
In a double-blind, descriptive study (Protocol 018), 302 pneumococcal vaccine-naïve adults ≥ 18 years of age living with HIV with CD4+ T-cell count ≥ 50 cells/µL and plasma HIV ribonucleic acid (RNA) < 50,000 copies/mL were randomized to receive either VAXNEUVANCE® or 13 valent pneumococcal polysaccharide conjugate vaccine, followed by PPV23 2 months later.

VAXNEUVANCE® elicited immune responses to all 15 serotypes contained in the vaccine as assessed by OPA GMTs and IgG GMCs at 30 days postvaccination. After sequential administration with PPV23, OPA GMTs and IgG GMCs were numerically similar between the two vaccination groups for all 15 serotypes.

Concomitant Vaccination
In a double-blind, randomized study (Protocol 021), 1,200 adults 50 years of age and older, with or without a history of prior PNEUMOVAX®23 vaccination, were randomized to receive VAXNEUVANCE® concomitantly or nonconcomitantly with seasonal inactivated quadrivalent influenza vaccine (QIV). One vaccination group received VAXNEUVANCE® and QIV concomitantly, followed by placebo 30 days later. A second vaccination group received QIV and placebo concomitantly, followed by VAXNEUVANCE® 30 days later.

VAXNEUVANCE® administered concomitantly with QIV is noninferior to VAXNEUVANCE® administered nonconcomitantly with QIV (based on a 2-fold non-inferiority margin, lower bound of the 2-sided 95% CI of GMT ratio>0.5), as assessed by pneumococcal OPA GMTs at 30 days postvaccination with VAXNEUVANCE® for all 15 serotypes contained in the vaccine. OPA GMTs were slightly lower for some serotypes when VAXNEUVANCE® was administered concomitantly with QIV compared to VAXNEUVANCE® administered alone. QIV administered concomitantly with VAXNEUVANCE® is noninferior to QIV administered nonconcomitantly (based on a 2-fold non-inferiority margin, lower bound of the 2-sided 95% CI of GMT ratio>0.5) as assessed by influenza strain-specific hemagglutination inhibition (HAI) GMTs at 30 days postvaccination with QIV for all 4 influenza strains.

15 MICROBIOLOGY

No microbiological information is required for this vaccine.

16 NON-CLINICAL TOXICOLOGY

General Toxicology: Repeat-dose toxicity studies in rats at doses up to 200 times the adult human dose on a mcg/kg basis, which included an evaluation of single-dose toxicity and local tolerance, revealed no

hazards to humans.

Carcinogenicity: VAXNEUVANCE® has not been evaluated for the potential to cause carcinogenicity.

Genotoxicity: VAXNEUVANCE® has not been evaluated for the potential to cause genotoxicity.

Reproductive and Developmental Toxicology:
Reproduction: VAXNEUVANCE® administered to female rats at a dose approximately 200 times the adult human dose on a mcg/kg basis had no effects on mating performance, fertility or embryonic/fetal survival.

Development: VAXNEUVANCE® administered to female rats at a dose approximately 200 times the adult human dose on a mcg/kg basis had no adverse effects on pre-weaning development. Antibodies to all 15 serotypes contained in VAXNEUVANCE® were detected in offspring, attributable to the acquisition of maternal antibodies via placental transfer during gestation and possibly via lactation.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

VAXNEUVANCE®
(Pneumococcal 15-valent Conjugate Vaccine [CRM_{197} Protein], adsorbed)

Read this carefully before you are given **VAXNEUVANCE®**. This leaflet is a summary and will not tell you everything about this vaccine. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **VAXNEUVANCE®**.

What is VAXNEUVANCE® used for?

- VAXNEUVANCE® is a vaccine for adults 18 years of age and older to help protect against invasive disease caused by 15 types of bacteria called pneumococcus. Invasive disease includes:
    - an infection in the blood.
    - an infection of the lungs (pneumonia) that comes with an infection in the blood.
    - an infection of the coverings of the brain and spinal cord (meningitis).

These illnesses are more likely to occur in older people and those with certain diseases or behaviors such as cigarette smoking.

VAXNEUVANCE® will not give you disease caused by pneumococcus.

VAXNEUVANCE® may not protect against diseases caused by types of pneumococcus that are not covered by the vaccine.

How does VAXNEUVANCE® work?
The vaccine works by helping your body to make its own antibodies which can protect you against pneumococcal disease caused by 15 types of pneumococcus.

What are the ingredients in VAXNEUVANCE®?
Medicinal ingredients: Bacterial sugars from 15 types of pneumococcus each linked to a protein (CRM_{197}) as the active ingredient. The sugars from these bacteria and the protein are not alive and do not cause disease.

Non-medicinal ingredients: Aluminum (aluminum phosphate is included to help the vaccine work better), L-histidine, polysorbate 20, sodium chloride and water. VAXNEUVANCE® does not contain any preservatives.

VAXNEUVANCE® comes in the following dosage form:

- 0.5 mL prefilled syringes

Do not use VAXNEUVANCE® if:

- You are allergic to any of the ingredients in VAXNEUVANCE® or to any vaccine containing diphtheria toxoid.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you get VAXNEUVANCE®. Talk about any health conditions or problems you may have or have had, including if you:

- have any allergies.
- have a fever. Your healthcare professional will tell you if you should receive VAXNEUVANCE®.
- have a weak immune system (which means your body has a hard time fighting off infections).
- take medicines or treatments that might weaken your immune system (like immunosuppressants or steroids).
- are pregnant or planning to become pregnant. Your healthcare professional will tell you if you should receive VAXNEUVANCE®.
- are breast-feeding or intend to breast-feed. Your healthcare professional will tell you if you should receive VAXNEUVANCE®.

Other warnings you should know about:
As with other vaccines, VAXNEUVANCE® may not fully protect all those who get it.

Use of VAXNEUVANCE® with other vaccines and medicines

Tell your healthcare professional if you are taking, have recently taken or might take any other vaccines or any medicines (for example, immunosuppressants or steroids which may make your immune system weak), including vitamins, minerals, natural supplements, alternative medicines or drugs that you can buy over the counter.

VAXNEUVANCE® can be given at the same time as the flu (inactivated influenza) vaccine

How is VAXNEUVANCE® given:

Usual dose:
Adult:
VAXNEUVANCE® is a shot that is usually given into the muscle (preferably in your upper arm).
You will receive one dose.

Children:
It has not yet been established whether VAXNEUVANCE® can be used in children and adolescents younger than 18 years of age.

Overdose:

If you think you, or a person you are caring for, have received too much VAXNEUVANCE®, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:
VAXNEUVANCE® is given as a single dose.

What are possible side effects from using VAXNEUVANCE®?
As with any vaccine, this vaccine can cause side effects, although not everybody gets them.

The most common side effects seen with VAXNEUVANCE® are:

- Pain, swelling or redness where you got the shot
- Feeling tired
- Muscle aches
- Headache
- Joint pain

These side effects are generally mild and last a short time.

Tell your healthcare professional about these side effects or any other unusual symptoms that develop after you receive this vaccine. Get medical care right away if you have symptoms of an allergic reaction, which may include:

- Wheezing or trouble breathing
- Swelling of the face, lips or tongue
- Hives
- Rash

These are not all the possible side effects you may have when taking VAXNEUVANCE®. There may be side effects that are not listed here. Ask your healthcare professional for more information.

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Suspected Side Effects for Vaccines

For the general public: Should you experience a side effect following immunization, please report it to your healthcare professional.
Should you require information related to the management of the side effect, please contact your healthcare professional. The Public Health Agency of Canada, Health Canada and Merck Canada Inc. cannot provide medical advice.

For healthcare professionals: If a patient experiences a side effect following immunization, please complete the Adverse Events Following Immunization (AEFI) Form appropriate for your province/territory (http://www.phac-aspc.gc.ca/im/aefi-essi-form-eng.php) and send it to your local Health Unit.

Storage:
Store refrigerated at 2°C to 8°C. Do not freeze. Protect from light.

Keep out of reach and sight of children.

If you want more information about VAXNEUVANCE®:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website:

https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the Merck Canada website www.merck.ca, or by calling 1-800-567-2594.

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